

A Mouse Model of *In Utero* Transplantation.

Journal: J Vis Exp

Publication Year: 2011

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PubMed link: 21307829

Funding Grants: Training Program in Stem Cell Research at UCSF

Public Summary:

The transplantation of stem cells into the fetus carries tremendous potential for treating a variety of inherited disorders in humans. For example, in utero transplantation (IUT) of blood stem cells has been used to successfully treat patients with severe immunodeficiencies. There are several instances, however, for which IUT in humans has not been successful. We have utilized a mouse model of IUT to study the biological sequelae of stem cell transplantation and the barriers that impede the success of IUT. In this scientific article and video, we describe a step-by-step approach to performing IUT in mouse fetuses and outline the critical steps and potential pitfalls of this technique. This approach can be used by other scientists who are interested in this method.

Scientific Abstract:

The transplantation of stem cells and viruses in utero has tremendous potential for treating congenital disorders in the human fetus. For example, in utero transplantation (IUT) of hematopoietic stem cells has been used to successfully treat patients with severe combined immunodeficiency.(1,2) In several other conditions, however, IUT has been attempted without success.(3) Given these mixed results, the availability of an efficient non-human model to study the biological sequelae of stem cell transplantation and gene therapy is critical to advance this field. We and others have used the mouse model of IUT to study factors affecting successful engraftment of in utero transplanted hematopoietic stem cells in both wild-type mice(4-7) and those with genetic diseases.(8,9) The fetal environment also offers considerable advantages for the success of in utero gene therapy. For example, the delivery of adenoviral(10), adeno-associated viral(10), retroviral(11), and lentiviral vectors(12,13) into the fetus has resulted in the transduction of multiple organs distant from the site of injection with long-term gene expression. in utero gene therapy may therefore be considered as a possible treatment strategy for single gene disorders such as muscular dystrophy or cystic fibrosis. Another potential advantage of IUT is the ability to induce immune tolerance to a specific antigen. As seen in mice with hemophilia, the introduction of Factor IX early in development results in tolerance to this protein.(14) In addition to its use in investigating potential human therapies, the mouse model of IUT can be a powerful tool to study basic questions in developmental and stem cell biology. For example, one can deliver various small molecules to induce or inhibit specific gene expression at defined gestational stages and manipulate developmental pathways. The impact of these alterations can be assessed at various timepoints after the initial transplantation. Furthermore, one can transplant pluripotent or lineage specific progenitor cells into the fetal environment to study stem cell differentiation in a non-irradiated and unperturbed host environment. The mouse model of IUT has already provided numerous insights within the fields of immunology, and developmental and stem cell biology. In this video-based protocol, we describe a step-by-step approach to performing IUT in mouse fetuses and outline the critical steps and potential pitfalls of this technique.

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